Title

Randomized Trial of Late Surfactant Treatment in Ventilated Preterm Infants Receiving Inhaled Nitric Oxide

Authors

Ballard, Roberta A
Keller, Roberta L
Black, Dennis M
et al.

Publication Date

2016

DOI

10.1016/j.jpeds.2015.09.031

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

J Pediatr. 2016 January ; 168: 23–29.e4. doi:10.1016/j.jpeds.2015.09.031.

Randomized Trial of Late Surfactant Treatment in Ventilated Preterm Infants Receiving inhaled Nitric Oxide

Roberta A. Ballard, M.D.[1], **Roberta L. Keller, M.D.**[1], **Dennis M. Black, Ph.D.**[2], **Philip L. Ballard, M.D., Ph.D.**[1], **Jeffrey D. Merrill, M.D.**[3], **Eric C. Eichenwald, M.D.**[4], **William E. Truog, M.D.**[5], **Mark C. Mammel, M.D.**[6], **Robin H. Steinhorn, M.D.**[7], **Elizabeth E. Rogers, M.D.**[1], **Rita M. Ryan, M.D.**[8], **David J. Durand, M.D.**[3], **Jeanette M. Asselin, MS RRT-NPS.**[3], **Catherine M. Bendel, M.D.**[9], **Ellen M. Bendel-Stenzel, M.D.**[10], **Sherry E. Courtney, M.D.**[11], **Ramasubbareddy Dhanireddy, M.D.**[12], **Mark L. Hudak, M.D.**[13], **Frances R. Koch, M.D.**[8], **Dennis E. Mayock, M.D.**[14], **Victor J. McKay, M.D.**[15], **T. Michael O'Shea, M.D.**[16], **Nicolas F. Porta, M.D.**[17], **Rajan Wadhawan, M.D.**[18], **Lisa Palermo, M.S.**[2], and **the TOLSURF study group**[*]

[1]Department of Pediatrics, University of California, San Francisco, San Francisco, CA

[2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California

[3]Children's Hospital and Research Center Oakland, Oakland, CA

[4]University of Texas Health Science Center- Houston, Houston, TX

[5]Children's Mercy Hospital, University of Missouri-Kansas City School of Medicine, Kansas City, MO

[6]Children's Hospital and Clinics of Minnesota, St. Paul, MN

[7]University of California Davis Children's Hospital, Sacramento, CA

[8]Medical University of South Carolina, Charleston, SC

[9]University of Minnesota Children's Hospital, Minneapolis, MN

[10]Children's Hospital and Clinics of Minnesota, Minneapolis, MN

[11]University of Arkansas for Medical Sciences, Little Rock, AR

[12]University of Tennessee Health Science Center, Memphis, TN

Correspondence: Roberta A. Ballard M.D., Suite 150, 3333 California St., San Francisco CA 9 4118; ballardr@peds.ucsf.edu; phone: 415 514 8139; fax: 415 502 1025.

[*]List of additional members of the TOLSURF Study Group are available at www.jpeds.com (Appendix 1).

The authors declare no conflicts of interest.

Portions of the study were presented as an abstract at the meetings of ATS, <city>, <state>, May <days>, 2014, and the European Academy of Pediatric Societies, <city>, <country>, October <days>, 2014.

Trial registration ClinicalTrials.gov: NCT01022580

[13]University of Florida College of Medicine-Jacksonville, Jacksonville, FL

[14]University of Washington, Seattle, WA

[15]All Children's Hospital, St. Petersburg, FL

[16]Wake Forest School of Medicine and Forsyth Medical Center, Winston-Salem, NC

[17]Northwestern University Feinberg School of Medicine, Chicago, IL

[18]Florida Hospital for Children, Orlando, FL

Abstract

Objectives—To assess whether late surfactant treatment of extremely low gestational age newborn (ELGAN) infants requiring ventilation at 7–14 days, who often have surfactant deficiency and dysfunction, safely improves survival without bronchopulmonary dysplasia (BPD).

Study design—ELGAN infants (≤ 28 0/7 weeks) who required mechanical ventilation at 7–14 days were enrolled in a randomized, masked controlled trial at 25 US centers. All infants received inhaled nitric oxide (INO) and either surfactant (calfactant/Infasurf®) or sham instillation every 1–3 days to a maximum of 5 doses while intubated. The primary outcome was survival at 36 weeks postmenstrual age (PMA) without BPD, evaluated by physiologic oxygen/flow reduction.

Results—Between January 2010 and September 2013, 511 infants were enrolled. There were no differences between treatment groups in mean birth weight (701±164 g), gestational age (25.2±1.2 weeks), percentage <26 weeks (70.6%), race, sex, severity of lung disease at enrollment, or co-morbidities of prematurity. Survival without BPD was not different between treated vs. controls at 36 weeks PMA (31.3% vs. 31.7%; relative benefit 0.98 (95% CI: 0.75, 1.28 p=0.89) or 40 weeks (58.7% vs. 54.1%; relative benefit 1.08:0.92, 1.27 p=0.33). There were no differences between groups in serious adverse events, co-morbidities of prematurity, nor in the severity of lung disease to 36 weeks.

Conclusions—Late treatment with up to 5 doses of surfactant in ventilated premature infants receiving iNO was well tolerated but did not improve survival without BPD at 36 or 40 weeks. Pulmonary and neurodevelopmental assessments are ongoing.

Bronchopulmonary dysplasia (BPD), initially described by Northway in 1967[(1)], is the most common form of chronic lung disease in children with an estimated 15,000 new cases annually in the United States. This condition affects infants born prematurely, is a major contributor to the $22 billion cost of prematurity each year, and is associated with long-term pulmonary disability, neurodevelopmental abnormalities and death. [(2–4)] With increased survival of extremely low gestational age infants (ELGANs, ≤28 wk gestation), another form of BPD has emerged that is characterized by impaired alveolar and microvascular development with excess tone and reactivity of airway smooth muscle. [(5–10)]

Despite antenatal glucocorticoid treatment to enhance lung maturation and replacement surfactant treatment at birth, as well as the more aggressive use of nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV), premature infants often need prolonged intubation and mechanical ventilation support and/or supplemental oxygen. When mechanical ventilation support is required beyond 7 days of

age, BPD occurs in more than 70% of surviving ELGANS.[11, 12] Factors contributing to BPD include structurally immature lungs, a compliant chest wall, deficiency and dysfunction of pulmonary surfactant, oxidant stress, immature respiratory drive, perturbed intrauterine environment, exposure to infection and inflammation and genetic susceptibility. Most of these infants experience clinical episodes of increased requirement for ventilatory support that are associated with dysfunctional surfactant, which is primarily due to low surfactant protein B (SP-B).[13] We and others have reported results from small studies of late surfactant treatment in premature infants who required ventilatory support beyond one week of life.[14–19] Surfactant treatment was well tolerated, with short-term improvement in Respiratory Severity Score (RSS=mean airway pressure x FiO_2) and SP-B content. [18, 19] However, in these pilot studies of late surfactant alone, there was no improvement in survival without BPD at 36 wk.

These observations provided the rationale for a large clinical trial of later doses of surfactant (TOLSURF) to prevent episodes of respiratory decompensation and BPD. In our prior study (NO CLD), a 25-day course of inhaled nitric oxide (iNO) started between 7 and 14 days of age at 20 ppm significantly improved survival without BPD at 36 and 40 wk as well as respiratory status to the age of 1 y [11, 20, 21]. iNO did not improve long term surfactant function[22] or markers of pulmonary inflammation and oxidative stress.[23, 24] For this multifactorial disorder, it is likely that a combination of treatments directed at different aspects of the pathogenesis will be needed to improve outcome. To address this question, we conducted a randomized trial of late surfactant vs. placebo sham procedure in premature infants receiving iNO.

METHODS

The Trial Of Late SURFactant (TOLSURF) was a masked, randomized, sham-controlled trial conducted in 25 US hospitals (ClinicalTrials.gov: NCT01022580). The study was designed to assess the effect of late doses of surfactant on BPD at 36 wk PMA in ELGANs (≤ 28 0/7wk) who required intubation and mechanical ventilation between 7 and 14 days of age and were receiving iNO. Infants were excluded if they had life threatening congenital abnormalities, were clinically unstable, had bilateral grade 4 IVH or were unlikely to be available for long-term pulmonary and neurodevelopmental follow-up.

The trial was conducted under the regulatory oversight of the FDA. IND # 79,367 for the combined use of calfactant with iNO, is held by the PI (RAB). The research protocol was approved by the IRBs of the participating institutions, and all parents signed a written informed consent. The consent included “opt-in/opt-out” permission for long-term banking of biospecimens and DNA. The consent was revised and reapproved by the DSMB and the IRBs after the NIH Consensus Conference on the use of iNO in preterm infants.[25] The NHLBI-appointed DSMB approved the protocol, informally reviewed safety data after every 60–80 infants were enrolled, and conducted two interim efficacy/futility analyses when both 36 and 40 week fully cleaned outcome information was available on 25% and 50% of the recruitment expectation of 524. The second futility analysis (conducted with complete outcome data for 301 infants [57% of 524]) was presented to the DSMB in August 2013, and at that time the DSMB recommended to NHLBI that the study be terminated, stating

that “based on a determination that the study treatment is very unlikely to demonstrate efficacy, the DSMB decided that continuation of study treatment intervention could no longer be justified” At the time of termination, although 511 of the planned 524 infants had been randomized, there were more than 200 for whom complete cleaned outcome data to 40 wk were not yet available.

For this trial we selected calfactant (Infasurf® ONY INC), a natural surfactant extracted from bovine lung lavage fluid, which has consistent amounts of SP-B (0.9% phospholipid) and SP-C (1.5% phospholipid). Standard clinical doses of calfactant were administered to treated infants by research staff behind a screen if the infants remained intubated (up to maximum of 5 doses). Control infants received a sham procedure (no intervention) behind the screen. Monitor and ventilator alarms were turned off during dosing to avoid unblinding of clinical staff. To accommodate research staff availability and infant instability, the dosing interval was not strictly set but could be repeated every 24 – 72 h up to 5 doses if the infant still required intubation. Dosing could be discontinued by physician request or parental withdrawal from the study. Clinical guidelines (Appendix 2; available at www.jpeds.com) for management of ventilation, including re-intubation, blood pressure management, and use of caffeine and postnatal corticosteroids were developed, presented at each clinical site and agreed to by investigators. All infants received iNO (Ikaria INC) according to the protocol used in the NOCLD trial.[11, 20] Although iNO therapy was accepted practice in the units participating in the trial, there was concern about the potential cost for families in light of the NIH Consensus Conference statement[25], and therefore the gas was provided at no charge by Ikaria INC (Hampton, NJ) to infants participating in the study. Blinding by treatment group is being maintained throughout the pulmonary and neurodevelopmental follow-up to age 2 years. Tracheal aspirate (TA) samples were collected prior to each dose of surfactant for analysis of surfactant and SP-B levels and later DNA isolation, and urine samples were collected at regular intervals for examination of NO metabolites. The content of SP-B in the large aggregate surfactant fraction was determined in baseline TA samples from a subpopulation of infants using published methodology [19] in order to assess whether enrolled infants had surfactant dysfunction and results will be published separately.

Patients were randomized to one of two groups: (1) sham instillation or (2) calfactant. Randomized permuted blocks of 4 stratified within clinical centers and gestational age groups, determined by obstetrical ultrasound (<26 or 26–28 wk 0 d), were used by the Data Coordinating Center (DCC) for randomization. The tables were sent to the Investigational Pharmacist at the sites. After eligibility was confirmed centrally by the project director, a study ID number was assigned and iNO begun. A masked syringe containing either calfactant or air was then sent to the unit and administered to the infant behind a screen by staff not involved in providing the infant’s clinical care. Cardiorespiratory and ventilator monitors were silenced. Control/sham infants had no procedure done behind the screen. Based on recommendations of the investigators and institutional review boards (IRBs), it was decided that a maximum of 5 additional doses of calfactant could be administered for the purpose of the study starting 48 h after initial clinical treatment.

We have found that parents of multiple births who participate in a clinical study have a strong preference that each of their children receives the same treatment. Therefore, the first

infant in a multiple birth was randomized according to the randomization schedule and subsequent infants were assigned to the same treatment group. This is equivalent to randomizing the mother and is accounted for in the analysis.[26]

STUDY EFFICACY ENDPOINTS

The primary outcome was survival without BPD at 36 wk PMA (ascertained at ±1wk). Infants discharged in room air before 36 wk were considered No BPD. Infants who required ventilatory support and any level of supplemental oxygen, or effective fraction of inspired oxygen (FiO2) >30% by nasal cannula (NC) were diagnosed with BPD ("severe" BPD by the NIH workshop definition).[2] Infants receiving mechanical ventilation, NCPAP, or >4 Liters NC flow in room air were assigned Yes BPD. Infants at 36 wk receiving ≤0.3 effective FiO2 at <2 L flow or on nasal flow <4 L with room air were evaluated for their requirement for respiratory support, determined by an oxygen/flow reduction (room air) challenge test.[27] The secondary outcome of BPD at 40 wk was defined in the same fashion for infants still in the hospital on support. Infants who were No BPD at 36 wk were imputed to be No BPD at 40 wk. Infants discharged on oxygen without a challenge test were assigned Yes BPD. The endpoints at 36 and 40 wk were determined by research staff not involved in dosing or clinical management of the infant and were monitored by the study project manager. Other secondary outcomes related to the severity of BPD: (1) pulmonary outcome at 12–24 months of age; and (2) neurodevelopmental outcome at 2 y of age are still being ascertained.

SAFETY

Known co-morbidities of prematurity including sepsis, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) that might potentially be affected by treatment were defined and tracked as potential adverse events (AEs). Death occurring within 7 days of completion of dosing required expedited reporting to the data safety monitoring board (DSMB) and FDA, with concurrent review by the independent study safety monitor. Other Serious Adverse Events (SAE's) reported at regular intervals included severe cardiopulmonary decompensation or increase in Respiratory Severity Score (RSS=MAPxFiO2) of >5 over baseline sustained >24 h within 4 h of a dosing procedure, severe pulmonary hemorrhage, pneumothorax requiring a chest tube, or significant unexpected events thought to be related to the study drug. Other adverse events (AE) were: (1) related to study drug dosing; (2) other complications including pulmonary hypertension or airway abnormalities; (3) complications related to tracheal aspirate sampling; (4) requirement for CPR involving cardiac medications and chest compression; or (5) unexpected events. Responses to the dosing procedure including transient bradycardia or desaturation were tracked on separate, blinded dosing tolerance forms and sent directly to the DCC.

STATISTICAL ANALYSES

The primary endpoint (survival to 36 wk without BPD) was analyzed as a dichotomous variable and compared between treatment groups. Effect size for outcomes were analyzed by generalized estimating equations (GEE) to account for clustering of multiple births within one mother. Infants with missing data for the primary outcome were assumed to have BPD

(n=2). Analyses were intention to treat: all randomized infants were included in the final analysis. Other analyses of baseline characteristics, SAE and AE used chi square or ANOVA without adjusting for clustering.

Two interim analyses (at 25% and 50% of completion) were planned for the DSMB including efficacy as well as futility analyses. Stopping boundaries using an alpha spending function resulted in a final adjusted significance level of 0.04695.[28]

To calculate power, we based incidence in the placebo group on a previous trial of iNO therapy[11, 20] that found 44% of the infants receiving iNO alone had 36-week BPD-free survival. We judged that a 13% absolute improvement in outcome (i.e. 44% vs. 57%) would be clinically important and lead to a change in practice. Using a 2-sided alpha level of 0.05 and power of 0.80, we calculated a total sample size requirement of 524.

RESULTS

Patients were enrolled from January 2010, to September 2013. At the time of initiating this study, most infants <28 wk with respiratory distress were intubated and treated with surfactant shortly after birth and extubated to NCPAP as rapidly as tolerated. There were 17 (3%) infants who were not initially intubated at birth and 121 who were extubated and then required re-intubation between 7 and 14 d. Infants who were still requiring intubation and mechanical ventilation or had been re-intubated between 7–14 d (46% of those screened) were evaluated for enrollment. The primary reasons available infants were excluded were: congenital malformation (22), clinically unstable (112), life expectancy <7d (23), bilateral Grade 4 IVH (33) or unlikely to be available for evaluation at 36 wk (44) (more than one reason in 46 infants). Of the 511 (53% of eligible) infants enrolled there were 252 and 259 infants randomized to the treated and control groups, respectively (Figure; available at www.jpeds.com). There was no difference between groups in BW (700 vs 702 grams), GA (25.2 vs 25.2 wk), percentage <26 wk (70.6% vs 70.7%), race, sex, proportion who had previously been extubated, severity of disease at enrollment, or co-morbidities of prematurity at baseline (Table I). There were fewer treated infants with a sibling in the study (17.5 treated vs 24.7% control p=0.05) and mothers of treated infants were younger (27.6 vs 29.5 years p=0.01) and had fewer years of education (p=0.05) (Table I).

OUTCOME

Survival without BPD was not different between treated vs. control groups at 36 wk (31.3% vs. 31.7%; relative benefit 0.98 (95%CI:0.75,1.28, p=0.89) or 40 wk (58.7% vs. 54.1%; relative benefit 1.08 (95%CI:0.92,1.27, p=0.33) (Table II). There was no difference in severity of lung disease as indicated by days of mechanical ventilation prior to 36 wk (38.1 vs. 37.3, p=0.60), days on supplemental oxygen (69.9 vs. 69.2, p=0.65) or treatment with systemic steroids (71.8% vs 78%, p=0.15) (Table II). There was no difference by treatment in infants of <26 wk or 26–28 wk. All of the infants who had BPD were classified as moderate to severe by the NIH workshop definition[2] with no difference in severity between groups (data not shown). Unexpectedly, the non-white infants trended toward better outcomes in both groups, with 37% versus 24% of non-white and white infants, respectively, surviving without BPD.

SAFETY

There were no differences in SAEs or co-morbidities of prematurity (AEs) occurring after enrollment (Table III). A total of 2293 doses/sham procedures were done (Table III). Infants were extubated as soon as possible; no infants remained intubated for the purpose of receiving additional doses. Nevertheless, the majority of both the treated and control infants continued to require intubation and received all 5 doses/sham procedures (78.2% and 81.9%, respectively). The intervention was discontinued in 23 infants either at physician request or parental withdrawal (Figure). All of the infants had episodes of transient bradycardia and oxygen desaturation during hospitalization and required re-intubation periodically. As expected, transient bradycardia (3.7% vs. 0.6% of procedures) and transient oxygen desaturation (11.7% vs 4.5% of procedures) were more frequent during the dosing procedure in the infants receiving late doses of surfactant. Fourteen treated vs 3 control infants (1.3% vs 0.25% of dosing/sham procedures) required re-intubation during the dosing period. Overall, the dosing procedure was well tolerated.

DISCUSSION

We found no beneficial effect of late surfactant as administered in TOLSURF on BPD-free survival at 36 or 40 wk PMA nor on the severity of BPD as defined by an NIH Workshop.[2] This trial of combination therapy of late doses of surfactant with iNO was designed to address several components of the multifactorial pathobiology of BPD. In animal models of BPD, treatment with iNO has been demonstrated to prevent increased airway resistance and muscularity[29, 30], to transiently improve surfactant function[22], and to improve lung growth, angiogenesis, and alveolarization[31]. Clinically, iNO increased survival without BPD and 1-year pulmonary status in one large clinical trial, [11, 20, 21] in which African American infants tended to respond better (P=0.055 for interaction) than whites. This trial, designed and initiated prior to the NIH consensus on the use of iNO in preterm infants, was based on the hypothesis that the combination of iNO with late doses of surfactant, given to address the known surfactant deficiency/dysfunction found in ventilated preterm infants after the first week of life[13], and confirmed in a subset of TOLSURF infants prior to the first dose, would shorten exposure to the volutrauma and oxidant stress of mechanical ventilation, thus decreasing the severity of early lung disease and subsequent diagnosis of BPD.

We found that the infants enrolled in this trial had a lower rate of survival without BPD at 36 wk (31%) than we had expected (44%) from our previous NO CLD study. Death before 36 wk was 5.8% in NO CLD and 7.8% in TOLSURF. We think the higher rate of BPD is likely due to the fact that the infants in TOLSURF were 1 wk earlier mean gestational age (25.2 vs 26 wk) with lower mean BW (700 vs 763 g) and, in addition, the infants had to be intubated to qualify for enrollment in TOLSURF, whereas in NO CLD infants could be on nasal CPAP at enrollment (thus TOLSURF infants had more compromised lung function initially).

It is possible that pulmonary outcome at term (40 wk) is more predictive of childhood lung disease secondary to prematurity than oxygen requirement at 36 wk. However, although improved over 36 wk, survival without BPD at 40 wk was similar for treated (59%) and

placebo (54%) infants. Treated infants did not have improved respiratory status with late surfactant, with approximately 80% of each group continuing to require intubation despite efforts to extubate to NCPAP or NIPPV and receiving the maximum allowed of 5 doses/sham treatments, with no difference between groups in time to successful tracheal extubation. If late surfactant had been effective in improving pulmonary status we would have expected treated infants to improve with dosing and tolerate extubation sooner. We found that late surfactant dosing was safe; in more than 2200 procedures, there were few problems, and there was no difference in mortality or adverse events between groups.

There are several possible explanations for the failure of late doses of surfactant to improve pulmonary outcome in this group of infants receiving iNO. The infants may not have had enough surfactant dysfunction to benefit from replacement. This is unlikely as we found in a subset of TOLSURF infants that levels of SP-B were low in most TA surfactants isolated prior to dosing (data not shown), similar to findings in a previous cohort [13]. There may have been irreversible lung damage due to volutrauma, inflammation, and oxidant stress prior to enrollment, which could not be completely addressed by iNO plus surfactant; these infants had already received a mean of 8.6 days of mechanical ventilation and oxygen exposure. The dose/frequency of replacement surfactant may have been inadequate. Although we gave the standard clinical dose of calfactant, it is possible that we would have had a better response to more frequent dosing over a longer period of time. We based our dosing on our pilot studies in which SP-B levels in TA surfactant returned to control levels <48 hours after calfactant instillation.[19]

Former preterm infants are at increased risk for persistent pulmonary morbidity including asthma and wheezing disorders. [3, 10, 32, 33] Longer term, meaningful clinical outcome is critical to understanding the value of interventions in the newborn period. In two studies of preventative treatments, later benefit was observed despite the absence of an effect on BPD at 36 wk PMA.[34, 35] We are following TOLSURF infants with pulmonary questionnaires collected every 3–6 months through 24 months corrected age and assessment of neurodevelopmental outcome at 24 months.

In conclusion, in this large randomized, masked study of late doses of surfactant combined with iNO, there was no difference in survival without BPD at 36 wk (preterm) with both groups demonstrating improved pulmonary outcome at 40 wk (term) PMA. Although late surfactant treatment transiently reduces the severity of lung disease, [14–19] our findings do not support this therapy as used in TOLSURF to prevent BPD at 36 wk. In ongoing laboratory studies we are evaluating the response to surfactant dosing and relationship to outcome to determine whether different timing or additional dosing might be beneficial. We are also determining the incidence of persistent pulmonary morbidity through at least 2 years of age to evaluate possible later risk or benefit. The observed safety of late surfactant dosing supports its potential use as a vehicle to deliver other medications such as corticosteroids directly to the lung.[36]

Acknowledgments

Supported by the National Institutes of Health/National Heart, Lung and Blood Institute (U01-HL094338 and U01HL094355) and the UCSF Clinical and Translational Sciences Institute (UL1TR000004). ONY, Inc provided

the Infasurf and IKARIA, Inc provided the inhaled nitric oxide, neither of which were involved in study design, collection, analysis, or interpretation of data, writing the manuscript or the decision to submit for publication.

We thank Nancy Newton MS RN CCRP, the project director for the first 4 years of the trial; Karin L. Knowles, for managing the administrative and regulatory aspects of the study and for help with preparation of the manuscript; the neonatal nurses, nurse practitioners, residents, fellows, and respiratory therapists who made this study possible; and to the families and infants who participated in the study.

Glossary

AE	Adverse events
BPD	Bronchopulmonary dysplasia
BW	Birth weight
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
ELGAN	Extremely low gestational age newborn (≤28 0/7wk)
FIO_2	Fraction of inspired oxygen
GA	Gestational age
GEE	Generalized estimating equations
iNO	Inhaled nitric oxide
IRB	Institutional Review Board
NC	Nasal cannula
NCPAP	Nasal continuous positive airway pressure
NHLBI	National Heart, Lung and Blood Institute
NIPPV	Nasal intermittent positive pressure ventilation
NO	Nitric Oxide
NO CLD	Inhaled Nitric Oxide to prevent Chronic Lung Disease trial
PMA	Post menstrual age
RSS	Respiratory severity score = mean airway pressure X FIO_2
SAE	Serious adverse events
SP-B	Surfactant Protein B
SP-C	Surfactant Protein C
TA	Tracheal aspirate
TOLSURF	Trial of Late Surfactant

References

1. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967; 276:357–68. [PubMed: 5334613]

2. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005; 116:1353–60. [PubMed: 16322158]

3. Hennessy EM, Bracewell MA, Wood N, Wolke D, Costeloe K, Gibson A, et al. Respiratory health in pre-school and school age children following extremely preterm birth. Archives of disease in childhood. 2008; 93:1037–43. [PubMed: 18562451]

4. Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD, et al. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. Early Hum Dev. 2012; 8:509–15. [PubMed: 22236557]

5. Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Human pathology. 1998; 29:710–7. [PubMed: 9670828]

6. Bancalari, E.; Gonzalez, A. Clinical course and lung function abnormalities during development of neonatal chronic lung disease. In: Bland, RD.; Coalson, JJ., editors. Chronic lung disease in early infancy. New York: Marcel Dekker; 2000. p. 41-64.

7. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001; 163:1723–9. [PubMed: 11401896]

8. Coalson JJ. Pathology of new bronchopulmonary dysplasia. Semin Neonatol. 2003; 8:73–81. [PubMed: 12667832]

9. Balinotti JE, Chakr VC, Tiller C, Kimmel R, Coates C, Kisling J, et al. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am J Respir Crit Care Med. 2010; 181:1093–7. [PubMed: 20133928]

10. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. Am J Respir Crit Care Med. 2010; 182:237–45. [PubMed: 20378729]

11. Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med. 2006; 355:343–53. [PubMed: 16870913]

12. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med. 2011; 183:1715–22. [PubMed: 21471086]

13. Merrill JD, Ballard RA, Cnaan A, Hibbs AM, Godinez RI, Godinez M, et al. Dysfunction of pulmonary surfactant in chronically ventilated premature infants. Pediatr Res. 2004; 56:1–9. [PubMed: 15152053]

14. Pandit PB, Dunn MS, Kelly EN, Perlman M. Surfactant replacement in neonates with early chronic lung disease. Pediatrics. 1995; 95:851–4. [PubMed: 7761208]

15. Bissinger R, Carlson C, Hulsey T, Eicher D. Secondary surfactant deficiency in neonates. J Perinatol. 2004; 24:663–6. [PubMed: 15229621]

16. Katz LA, Klein JM. Repeat surfactant therapy for postsurfactant slump. J Perinatol. 2006; 26:414–22. [PubMed: 16724122]

17. Laughon M, Bose C, Moya F, Aschner J, Donn SM, Morabito C, et al. A pilot randomized, controlled trial of later treatment with a peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. Pediatrics. 2009; 123:89–96. [PubMed: 19117865]

18. Merrill JD, Ballard PL, Courtney SE, Durand DJ, Hamvas A, Hibbs AM, et al. Pilot trial of late booster doses of surfactant for ventilated premature infants. J Perinatol. 2011; 31:599–606. [PubMed: 21311500]

19. Keller RL, Merrill JD, Black DM, Steinhorn RH, Eichenwald EC, Durand DJ, et al. Late administration of surfactant replacement therapy increases surfactant protein-B content: a randomized pilot study. Pediatr Res. 2012; 72:613–9. [PubMed: 23037875]

20. Ballard RA. Inhaled nitric oxide in preterm infants---correction. New Engl J Med. 2007; 357:1444–45. [PubMed: 17914048]

21. Hibbs AM, Walsh MC, Martin RJ, Truog WE, Lorch SA, Alessandrini E, et al. One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial. J Pediatr. 2008; 153:525–9. [PubMed: 18534620]

22. Ballard PL, Merrill JD, Truog WE, Godinez RI, Godinez MH, McDevitt TM, et al. Surfactant function and composition in premature infants treated with inhaled nitric oxide. Pediatrics. 2007; 120:346–53. [PubMed: 17671061]
23. Truog WE, Ballard PL, Norberg M, Golombek S, Savani RC, Merrill JD, et al. Inflammatory markers and mediators in tracheal fluid of premature infants treated with inhaled nitric oxide. Pediatrics. 2007; 19:670–8. [PubMed: 17403837]
24. Ballard PL, Truog WE, Merrill JD, Gow A, Posencheg M, Golombek SG, et al. Plasma biomarkers of oxidative stress: relationship to lung disease and inhaled nitric oxide therapy in premature infants. Pediatrics. 2008; 121:555–61. [PubMed: 18310205]
25. Cole FS, Alleyne C, Barks JD, Boyle RJ, Carroll JL, Dokken D, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. 2011; 127:363–9. [PubMed: 21220405]
26. Hibbs AM, Black D, Palermo L, Cnaan A, Luan X, Walsh M, et al. Accounting for Multiples Births in Neonatal and Perinatal Trials – Systematic Review and Case Study. J Pediatrics. 2010; 156:202–8.
27. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol. 2003; 23:451–6. [PubMed: 13679930]
28. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979; 35:549–56. [PubMed: 497341]
29. Martin RJ, Mhanna MJ, Haxhiu MA. The role of endogenous and exogenous nitric oxide on airway function. Semin Perinatol. 2002; 26:432–8. [PubMed: 12537315]
30. Bland RD, Albertine KH, Carlton DP, MacRitchie AJ. Inhaled nitric oxide effects on lung structure and function in chronically ventilated preterm lambs. Am J Respir Crit Care Med. 2005; 172:899–906. [PubMed: 15976381]
31. Lin YJ, Markham NE, Balasubramaniam V, Tang JR, Maxey A, Kinsella JP, et al. Inhaled nitric oxide enhances distal lung growth after exposure to hyperoxia in neonatal rats. Pediatr Res. 2005; 58:22–9. [PubMed: 15879297]
32. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax. 2013; 68:760–6. [PubMed: 23604458]
33. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS medicine. 2014; 11:e1001596. [PubMed: 24492409]
34. Davis JM, Parad RB, Michele T, Allred E, Price A, Rosenfeld W. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. Pediatrics. 2003; 111:469–76. [PubMed: 12612223]
35. Zivanovic S, Peacock J, Alcazar-Paris M, Lo JW, Lunt A, Marlow N, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med. 2014; 370:1121–30. [PubMed: 24645944]
36. Yeh TF, Lin HC, Chang CH, Wu TS, Su BH, Li TC, et al. Early intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. Pediatrics. 2008; 121:e1310–8. [PubMed: 18426851]

APPENDIX

In addition to the authors, the following members of the TOLSURF Study Group participated in this study:

University of California San Francisco, CA: S. Hamilton Strong, J. Immamura-Ching, M. Orfanos-Villalobos, C. Williams; Alta Bates Summit Medical Center, Berkeley, CA, and Children's Hospital and Research Center Oakland, Oakland, CA: D. Horton, L. Pacello, A. Willard; Children's Mercy Hospital, Kansas City, MO: C. Gauldin, A. Holmes, P. Johnson,

K. Meinert; Women and Children's Hospital of Buffalo, Buffalo, NY: A.M. Reynolds, MD, J. Lucie, P. Conway, M.l. Sacilowski, M. Leadersdorff, P. Orbank, K. Wynn; Anne and Robert H. Lurie Children's Hospital/Northwestern University, Chicago, IL: M. deUngria MD, J. Khan MD, K. Hamann, M. Schau, B. Hopkins, J. Jenson; Texas Children's Hospital, Houston, TX: C. Garcia; Stonybrook University Hospital, Stonybrook, NY: J. Shariff, R.McGovern,J. Adelman, A. Combs, M. Tjersland, University of Washington, Seattle, WA: S. Walker, E. Howland, J. Longoria, H. Meo; University of Texas Health Science Center, Houston, TX: G. McDavid, K. Burson, R. Hinojosa, C. Johnson, K. Miller, S. Rogers, S. Wright; University of Florida College of Medicine, Jacksonville, UF Jacksonville, and Wolfson Children's Hospital, Jacksonville, FL:K. Barnette, A. Kellum, M. Burke, C. Hayes, S. Chadwick, D. Howard, C. Kennedy, R. Prince; Wake Forest School of Medicine and Forsyth Medical Center, Winston Salem, NC: B. Stefanescu MD, J. Helderman, MD, K. Warden, P. Brown, J. Griffin, L. Conley; University of Minnesota Children's Hospital, Minneapolis, MN: M. Georgieff, M.D., B. Davern, M. Mills, S. Ritter; Medical University of South Carolina, Charleston, SC: C. Wagner, MD, D. Fanning, J. Roberson; Children's Hospitals and Clinics of Minnesota, St. Paul, MN: A. Lampland, MD, P. Meyers, A. Brey; Children's Hospitals and Clinics of Minnesota, Minneapolis, MN: C. Worwa, P. Dixon, G. Ebert, C. Hejl, M. Maxwell, K. McCullough; University of Tennessee Health Science Center, Memphis, TN: MT. El Abiad, MD, A. Talati, MD, S. Dempsey, K. Gammage, G. Gower, K. James, P. LeNoue; All Children's Hospital, St. Petersburg, FL: S. Bell, D. Bruton, M. Beaulieu, R. Williams; Florida Hospital for Children, Orlando, FL: R. Barron-Nelson, S. Taylor; Arkansas Children's Hospital and University of Arkansas Medical Sciences, Little Rock, AK: N. C. Sikes, G. Lowe, B. Proffitt;

Clinical Coordinating Center – University of California San Francisco, Department of Pediatrics, CA: C. Chapin, H. Horneman, K. Hamann, S. Kelley.

Data Coordinating Center **–** University of California San Francisco, Department of Epidemiology and Biostatistics, CA: E. Vittinghoff, PhD, J. Hietpas, L. Denton, L. Wu.

Data Safety Monitoring Board **–** Cincinnati Children's Hospital Medical Center, Cincinnati, OH: A. Jobe MD, (Chair 2009–2010); UH Rainbow Babies and Children's Hospital, Cleveland, OH: A. Fanaroff MD (Chair 2010–2014); EMMES Corporation, Rockville, MD: T. Clemons; Boston University School of Public Health, Boston, MA: L. Glantz; Wake Forest School of Medicine, Winston-Salem, NC: D. Reboussin; Stanford University, Stanford, CA: K. Van Meurs MD (2009–2010); Johns Hopkins University, Baltimore, MD: M. Allen MD (2010–2014); Women and Infants Hospital, Providence, RI: B. Vohr MD.

Clinical Steering Committee--R. Ballard, MD, P. Ballard, MD, PhD, C. Blaisdell, MD, D. Durand, MD, D. Black, PhD, E. Eichenwald, MD, R. Keller, MD, M. Mammel, MD, J. Merrill, MD, E. Rogers, MD, R. Ryan, MD, W. Truog, MD, J. Asselin, N.Newton.

Appendix 2. TOLSURF CLINICAL GUIDELINES 2010

24.0 APPENDIX B CLINICAL MANAGEMENT GUIDELINES

24.1 Guidelines for ventilation & oxygenation

Oxygen saturation limits (until 32 weeks' PMA)

1. Target saturations 85–94%
2. Set saturation monitor limits (depending on individual center saturation targets)
    a. Lower: 80–85%
    b. Upper: 92–95%

Mechanical ventilation guidelines—conventional ventilation

1. Appropriate PEEP to maintain lung inflation. Usually 5–7 cmH_2O.
2. Tidal volume 3–7 mL/kg (usually 4–6)
3. PCO_2 target 45–70 mmHg
4. pH target ≥ 7.15 (most want >7.20)

Suggested criteria for reintubation (until 32 weeks' PMA)

Note: some patients, particularly if unstable or with increased work of breathing may be re-intubated earlier

1. Inability to maintain target saturation despite NCPAP > 8, nasal ventilation or high flow nasal cannula > 3 liters per minute with FIO2 > 0.6
2. PCO_2 consistently > 70 mmHg
3. pH consistently < 7.15
4. Recurrent or severe (requiring bag mask ventilation) apnea despite maximal caffeine therapy and NCPAP

24.2 Guidelines for caffeine citrate use

Caffeine citrate therapy should be considered for infants with gestational age less than 31 weeks, who are less than 10 days of age and require mechanical ventilation or CPAP, for the following indications: apnea prophylaxis, apnea treatment, facilitation of extubation.

Recommended regimens

1. Caffeine citrate IV/PO load 20 mg/kg/dose x1
2. Caffeine citrate maintenance IV/PO 5–10 mg/kg/dose once daily until 32–34 weeks post menstrual age even if infant remains intubated.

Considerations

1. If central apnea occurs / persists on caffeine therapy and other causes of apnea have been ruled out, then caffeine dose may be adjusted by increasing the maintenance dose by 1–3 mg/kg/dose (if HR < 180) to a maximum maintenance dose of 10 mg/kg/dose. In addition, one may also consider an additional caffeine bolus of 10mg/kg. When adjusting caffeine dose, give the bolus immediately regardless of timing of the last maintenance dose. Base timing of subsequent doses from the time the bolus is administered.

2. Schmidt B et al. Caffeine therapy for apnea of prematurity. NEJM 2006; 354:2112–2121.

3. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, Sinha S, Tin W; for the Caffeine for Apnea of Prematurity Trial Group. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. J Pediatr. 2009 Nov 17. [Epub ahead of print]

24.3 Guidelines for glucocorticoids for lung disease

Potential candidates for initiation of glucocorticoids—***try to avoid administration!***

1. Infants at least 2 weeks of age
2. Other therapies optimized
3. RSS ≥ 7 (RSS = MAP x FiO_2)
4. No contraindications to glucocorticoid therapy
   a. Indomethacin exposure within 48h
   b. Systemic hypertension
   c. Active infection with < 24 hours of appropriate antibiotics

Regimen guidelines (**short course**)

1. Hydrocortisone (total dose 5 mg/kg)

   Day 1 – 3 mg/kg/d divided q 12h

   Day 2 – 1.5 mg/kg/d divided q 12h

   Day 3 – 0.5 mg/kg/d divided q 12h

2. Dexamethasone (total dose 0.45 mg/kg = HC 6.75–9 mg/kg (15 – 20x))

   Day 1 – 0.2mg/kg/d divided q12h

   Day 2 – 0.15 mg/kg/d divided q12h

   Day 3 – 0.1 mg/kg/d divided q12h

Regimen guidelines (**long course**)

Note: Discontinue or rapid taper (½ dose x 24h, ¼dose x 24h then off) if no response after 48h. Response defined as ability to wean ventilator and oxygen.

1. Hydrocortisone (total dose 15 mg)

   Day 1–3 – 3 mg/kg/d divided q 12h

   Day 4–6 – 1.5 mg/kg/d divided q 12h

   Day 7–9 – 0.5 mg/kg/d divided q 12h

2. Dexamethasone (total dose 0.89 mg/kg = HC 13.35–17.8 mg/kg (15–20x))

   Day 1–3 – 0.15 mg/kg divided q 12h

   Day 4–6 – 0.1 mg/kg/d divided q 12h

   Day 7–8 – 0.05 mg/kg/d divided q 12h

   Day 9–10 – 0.02 mg/kg/d divided q 12h

Considerations

1. If infant requires surgery while on steroid course, consider stress dose hydrocortisone 2–4 mg/kg/d divided q 6–12h × 24h
2. If infant develops hypotension or other signs of adrenal insufficiency after completion of steroid course, go back on most recent dose x 24h, then taper to ½ dose x 24h and then ¼ dose x 24h
3. May repeat short course at 7–10d if infant meets criteria

24.4 Guidelines for glucocorticoids for hypotension

Potential candidates for initiation of glucocorticoids for hypotension

1. Inadequate response to vasopressor therapy (dopamine ≥ 20 mcg/kg/min ± dobutamine or epinephrine) with *either*
   a. persistent hypotension despite fluid resuscitation, or
   b. inability to wean medications for > 48h
2. No contraindications to glucocorticoid therapy
   a. Indomethacin exposure within 48h
   b. Active infection with < 24 hours of appropriate antibiotics

Regimen guidelines

1. Hydrocortisone (total dose 5 mg/kg). Some infants may respond to initial 1–2 doses, making further dosing unnecessary.

   Day 1 – 1–2 mg/kg/d divided q 8–12h

   Day 2 – 1 mg/kg/d divided q 8–12h

   Day 3 – 0.5 mg/kg/d divided q 12h

Considerations

1. If infant requires surgery while on steroid course, consider stress dose hydrocortisone 2–4 mg/kg/d divided q 6–12h × 24h
2. If infant develops hypotension or other signs of adrenal insufficiency after completion of steroid course, go back on most recent dose x 24h, then taper to ½ dose x 24h and then ¼ dose x 24h, then discontinue.

24.5 Guidelines for Vitamin A therapy (if being used)

Candidates for initiation of Vitamin A

1. All infants < 1000 g birth weight
2. Infants 1000–1250 g birth weight if ventilated > 24h

Dosing regimen

5000 Units IM every M, W, F x 4 weeks

May be discontinued prior to 4 weeks of treatment if infant reaches full enteral feeds (150 mL/kg of premature formula or fortified breast milk or 120 mL/kg of premature formula with 1 mL/d Poly-Vi-Sol)

Vitamin A use should be consistent among all infants at any site.

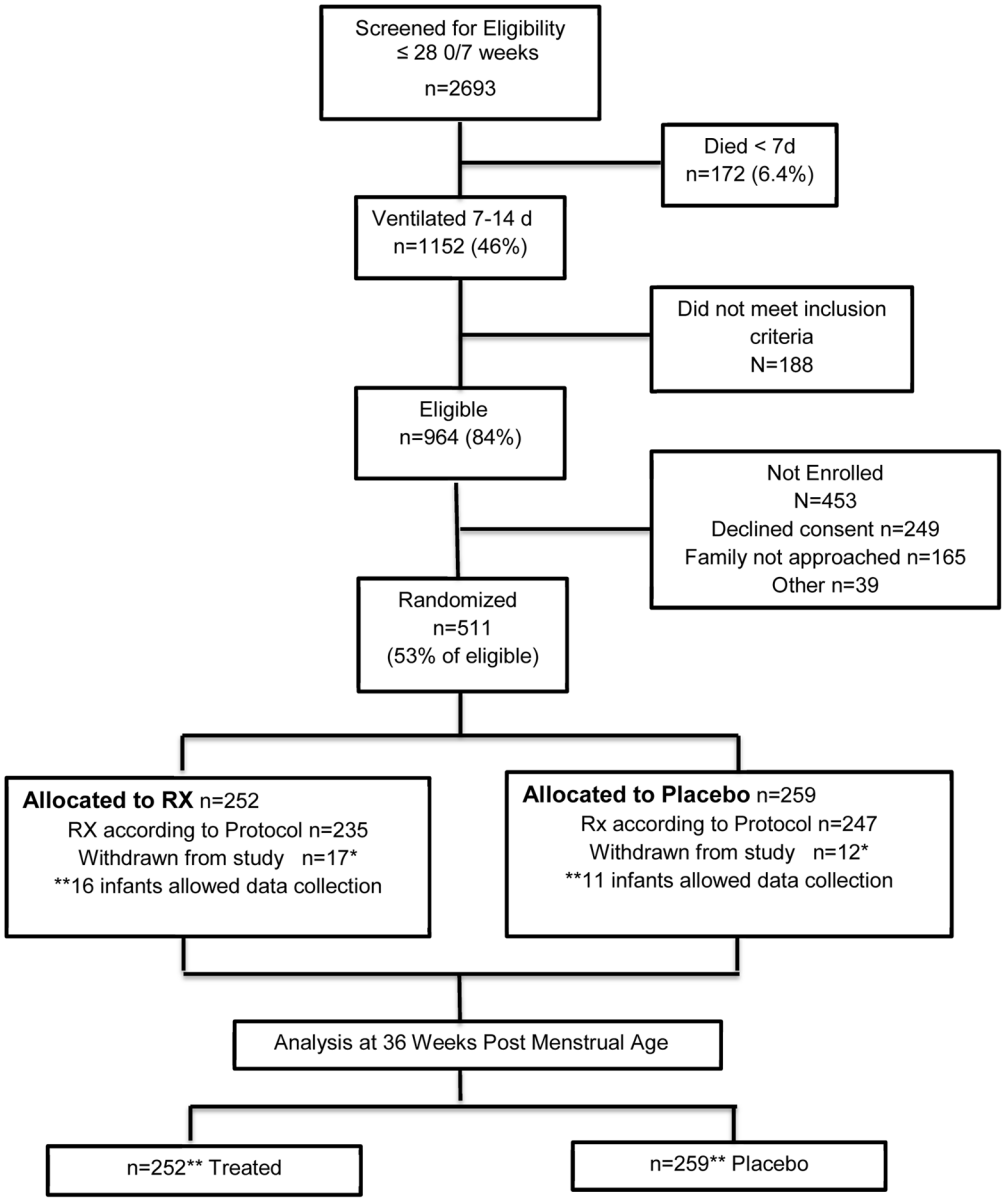

Figure 1. Consort Diagram for TOLSURF showing enrollment and completion of data for the two study groups

* Withdrawn resulted in no further treatment with either iNO or Infasurf

** One infant in each group with no data, 36 weeks outcome unknown = Yes BPD

Table 1

Baseline Characteristics *

Characteristics of Infants	Late Surfactant	Control	P value
N	252	259	
Gestational Age			
Mean/SD -weeks	25.2 ± 1.2	25.2 ± 1.2	0.70
< 26 weeks no. (%)	178 (70.6)	183 (70.7)	
26–28 weeks no. (%)	74 (29.4)	76 (29.3)	
Birth weight			0.88
Mean/SD - g	700.1±173.2	702.3 ±156.0	
< 750 no. (%)	163 (64.7)	162 (62.5)	
≥ 750 no. (%)	89 (35.3)	97 (37.5)	
IUGR Percentile			0.19
≤ 10 no. (%)	49 (19.4)	39 (15.1)	
> 10 no. (%)	203 (80.6)	220 (84.9)	
Male sex no. (%)	143 (56.7)	138 (53.3)	0.43
Mother's Race / Ethnic Group no. (%)*			0.31
White	116 (46.0)	128 (49.4)	
African American	98 (38.9)	90 (34.7)	
Hispanic	23 (9.1)	33 (12.7)	
Other	15 (6)	8 (3.1)	
Antenatal Corticosteroids no. (%)	216 (85.7)	224 (86.5)	0.12
Cesarean delivery no. (%)	175 (69.4)	195 (75.3)	0.14
Surfactant at birth no. (%)	251 (99.6)	258 (99.6)	1.0
Multiple Birth – siblings enrolled in study			
no. (%)	44 (17.5)	64 (24.7)	0.05
Age at entry mean/SD - days	10.4±2.4	10.4±2.4	0.79
Respiratory Severity Score (RSS) prior to enrollment **			
Mean/SD	3.7 ± 2.3	3.8± 2.2	0.47
Median (Interquartile range)	3.0 (2.2–4.4)	3.2 (2.3–4.8)	0.47
Vent Mode prior to enrollment no. (%)			0.20
Conventional no. (%)	152 (60)	169 (65)	
High Frequency no. (%)	99 (39)	87 (34)	
Comorbidities prior to enrollment no. (%)***			
Pneumothorax w/chest tube no. (%)	10 (4.0)	9 (3.5)	0.77
Pulmonary hemorrhage no. (%)	15 (6.0)	10 (3.9)	0.27
PDA no. (%)	85 (33.7)	94 (36.3)	0.83
PDA ligation no. (%)	8 (3.2)	6 (2.3)	0.84
NEC no. (%)	3 (1.2)	1 (0.4)	0.22
NEC/Perforation requiring surgery no. (%)	3 (1.2)	1 (0.4)	0.31
Isolated GI perforation no. (%)	13 (5.2)	7 (2.7)	0.15
Sepsis -CSF or Blood no. (%)	21(8.3)	26 (10)	0.49

Characteristics of Infants	Late Surfactant	Control	P value
Intraventricular hemorrhage			0.72
Grade 1 or 2 no. (%)	54 (21.4)	64 (24.7)	
Grade 3 or 4 no. (%)	42 (16.7)	36 (13.9)	
Maternal Characteristics	**Late Surfactant**	**Control**	**P value**
Maternal age mean/SD years	27.6 ± 6.2	29.5 ± 6.6	0.001
Maternal Education no. (%)			0.048
< high school no. (%)	26 (10.3)	36 (13.9)	
high school +/or some college no. (%)	139 (55)	111 (43)	
college graduate +/or grad school no. (%)	74 (29.4)	97 (37)	
Unknown no. (%)	13 (5.2)	15 (5.8)	

* Race or ethnic group was self-reported by the mother of the infant

** The respiratory severity score was calculated as the fraction of inspired oxygen multiplied by the mean airway pressure (in centimeters of water)

*** PDA was reported only if infant had treatment with either indomethacin or Ibuprofen or surgical closure was provided. Necrotizing enterocolitis was diagnosed by the presence of pneumatosis, hepatobiliary gas, or pneumoperitoneum on radiography, plus one or more of the following symptoms: bilious gastric aspirate or emesis, abdominal distension, or occult blood in the stool. Sepsis was diagnosed by a positive culture of blood or spinal fluid treated for at least 7 days.

Table 2

Outcome to 36 and 40 weeks

Variable	Late Surfactant	Control	Relative Benefit (95%CI)*	P value
N	252	259		
BPD at 36 weeks**				
Survival without BPD no. (%)	79 (31.3)	82 (31.7)	0.98 (0.75, 1.28)	0.89
Death or Survived with BPD no. (%)	173 (68.7)	177 (68.3)		
BPD no. (%)	155 (61.5)	155 (59.8)		
Died no. (%)	18 (7.1)	22 (8.5)		
Gestational age < 26 weeks - n	178	183		
Survival without BPD no. (%)	52 (29.2)	56 (30.6)	0.94 (0.68, 1.31)	0.72
Death or Survived with BPD no. (%)	126 (71)	127 (69.4)		
BPD no. (%)	110 (61.8)	109 (59.6)		
Died no. (%)	16 (9.0)	18 (9.8)		
Gestational age 26–28 weeks – n	74	76		
Survival without BPD no. (%)	27 (36.5)	26 (34.2)	1.06 (0.69, 1.65)	0.78
Death or Survived with BPD no. (%)	47 (63.5)	50 (65.8)		
BPD no. (%)	45 (60.8)	46 (60.5)		
Died no. (%)	2 (2.7)	4 (5.3)		
Respiratory Outcomes to 36weeks				
Number Discharged ≤ 36 weeks	4	7		
Discharged in room air no. (%)	3 (75.0)	2 (28.6)		
Discharged on oxygen no. (%)	1 (25.0)	5 (71.4)		
Discharged on ventilator w trach no. (%)	0	0		
Days of mech ventilation mean/SD	38.1 ±18.4	37.3±16.6		0.60
Days on oxygen mean/SD	69.9 ± 16.8	69.2 ± 15.8		0.65
Treat with systemic steroids no. (%)	181 (71.8)	202 (78.0)		0.15
BPD at 40 weeks				
Survival without BPD no. (%)	148 (58.7)	140 (54.1)	1.08 (0.92,1.27)	0.33
Death or Survived with BPD no. (%)	104 (41.2)	119 (45.9)		
BPD no. (%)	83 (32.9)	96 (37.1)		
Died no. (%)	21 (8.3)	23 (8.9)		
Gestational age < 26 weeks - N	178	183		
Survival without BPD no. (%)	102 (57.3)	97 (53.0)	1.08 (0.89,1.30)	0.46
Death or Survived with BPD no. (%)	76 (42.7)	86 (47.0)		
BPD no. (%)	57 (32.0)	68 (37.2)		
Died no. (%)	19 (10.7)	(18 (9.8))		
Gestational age 26–28 weeks – N	74	76		
Survival without BPD no. (%)	46 (62.2)	43 (56.6)	1.11 (0.83,1.48)	0.47
Death or Survived with BPD no. (%)	28 (37.8)	33 (43.4)		
BPD no. (%)	26 (35.1)	28 (36.8)		
Died no. (%)	2 (2.7)	5 (6.6)		

Variable	Late Surfactant	Control	Relative Benefit (95%CI)*	P value
Respiratory Outcomes to 40 weeks				
Number Discharged ≤ 40 weeks	85	92		
Discharged in room air no. (%)	57 (67.1)	51 (55.4)		
Discharged on oxygen no. (%)	28 (33.0)	41 (44.6)		

* CI denotes confidence interval

** Primary Outcome

Table 3

Comorbidities and dosing tolerance after entry

	Late Surfactant	Control	P value
N	252	259	
Pneumothorax with chest tube	2 (0.8)	2 (0.8)	0.98
Pulmonary hemorrhage	1 (0.4)	0 (0.0)	0.31
Pulmonary hypertension	25 (9.9)	28 (10.8)	0.74
PDA	89 (36.5)	95 (37.5)	0.80
PDA ligation	55 (22.5)	51 (20.2)	0.51
NEC, new/worsened			0.59
without surgery	14 (5.6)	6 (2.3)	
requiring surgery	13 (5.2)	18 (6.9)	
Sepsis (blood or CSF)	72 (28.6)	69 (26.6)	0.63
Tracheal stenosis	3 (1.2)	6 (2.3)	0.33
Vocal cord paralysis	4 (1.6)	5 (1.9)	0.77
Intraventricular hemorrhage, new/worsened			0.89
Grade 1 or 2	16 (6.3)	23 (8.9)	
Grade 3 or 4	17 (6.7)	12 (4.6)	
ROP	198 (78.6)	198 (76.4)	0.57
Surgery	34 (13.5)	29 (11.2)	0.28
Intravitreal bevacizumab	16 (6.7)	24 (9.5)	0.009
Dosing Tolerance			
Number of procedures	1115	1178 (sham)	
Received 5 doses no. (%)	197 (78.2)	212 (81.9)	
Severe respiratory decomp** no. (%)	1 (0.4)	2 (0.8)	0.57
Reintubation ** n (% of procedures)	14 (1.3)	3 (0.3)	
Bradycardia** n (% of procedures)	41 (3.7)	7 (0.6)	
Desaturation** no. (%)	130 (11.7)	53 (4.5)	
Pneumothorax no. (%)	1 (0.4)	1 (0.4)	0.99
Days 1st procedure to 1st extubation mean/SD	24±18	24±20	

* Dosing was not associated with pulmonary interstitial emphysema, pulmonary hemorrhage or cardiorespiratory decompensation requiring CPR

** Findings during dosing procedure only